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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/211,312	07/01/94	LABIGNE A	6800750XP

EXAMINER

18M1/0812

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ART UNIT	PAPER NUMBER
1817	20

DATE MAILED: 08/12/97

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 5-5-97

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-18, 20-36, 40-61 is/are pending in the application.
Of the above, claim(s) 1-17, 20-36 is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 40-61 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☒ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

DETAILED ACTION

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1817.

1. Since this application is eligible for the transitional procedure of 37 CFR 1.129(a), and the fee set forth in 37 CFR 1.17(r) has been timely paid, the finality of the previous Office action is hereby withdrawn pursuant to 37 CFR 1.129(a). Applicant's first submission after final filed on January 21, 1997 (and same amendment filed May 5, 1997) has been entered.

2. Claims 18, 19 and 37-39 have been canceled. New claims 40-61 have been added. Claims 40-61 are now pending in the present application. The previous rejections have been withdrawn with the exception of those specifically discussed below.

3. This application contains claims 1-17 and 20-36 drawn to an invention non-elected with traverse in Paper No. 10. A complete response to the final rejection must include cancellation of non-elected claims or other appropriate action (37 CFR 1.144) MPEP § 821.01.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. Claims 40-61 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are indefinite for being in improper Markush format. The Office recommends the use of the phrase "selected from the group consisting of..." with the use of the conjunction "and" rather than "or" in listing the species. See MPEP 706.03(Y). Claims 53-58

are vague and indefinite in the recitation of "antibody" as it is not clear if it is a polyclonal or monoclonal antibody.

6. The objection to the specification and rejection of claims 40-61 under 35 U.S.C. § 112, first paragraph (i.e. lack of an enabling disclosure) is maintained. This rejection is maintained for essentially the same reasons as the rejection under this statutory provision, as set forth in the last Office action. Applicants' arguments filed January 21, 1997 and May 5, 1997 have been fully considered but they are not deemed to be persuasive.

The following is a quotation of the first paragraph of 35 U.S.C. § 112: The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention. The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure. Claims 56-61 are directed to compositions comprising the polypeptide or antibodies that bind these polypeptides and a pharmaceutically acceptable carrier. Although not specifically claimed the specification teaches that the compositions will be used to treat infection due to *H. pylori*. However, the specification is not enabled for nor has taught one of skill in the art how to use such compositions for this intended purpose. It is noted that the art teaches that "[W]ith the exception of UreA and UreB structural polypeptides of the enzyme, no role can as yet be assigned to the nine proteins encoded by the *H. pylori* urease gene cluster." (Cussac et al. 1992, abstract). Therefore it is unclear how the products, polypeptides, from these genes can be used in compositions to treat infection due to *H. pylori*. Further, Houghten et al. teach that changes/ modifications (addition, substitution, deletion or inversion) of one or more amino acids in a polypeptide will alter antigenic

determinants and therefore effect antibody production (p. 21). Houghten et al. also teach that "... combined effects of multiple changes in an antigenic determinant could result in a loss of [immunological] protection." and "A protein having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new antigen that is precipitously or progressively unrecognizable by any of the antibodies..." (p. 24). It is not always possible to make antibodies or protect against infection if the antigenic determinants have been altered. Applicants propose to make recombinant strains using mutations in the Ure genes and then use these in compositions, however as set forth above it is unclear if changes/modifications that occur in the gene will effect the antigenic determinants; i.e. are the determinants maintained in order to obtain a composition. Further, the antigenic determinants or epitopes have not been disclosed for the *H. pylori* urease. The specification has not taught the use of fragments; how to obtain these fragment or how much of the polypeptide constitutes a fragment. What is the minimal portion that is needed for the polypeptide to remain functional? In view of the reasons set forth, there would be undue experimentation for a skilled artisan to practice the claimed invention.

Applicants have asserted that the present specification provides antibodies and polypeptides that provide therapeutic benefits. However, it is noted that there is no known function of the presently claimed polypeptides that Applicants used for the antibody preparation and polypeptides claimed to treat infection due to *H. pylori*. The primary claims (18 and 19) recite that the polypeptides can have modifications and as taught by Houghten these modifications can change or alter antigenic determinants and therefore effect antibody production (p. 21). Houghten et al. also teach that "... combined effects of multiple changes in an antigenic determinant could result in a loss of [immunological] protection." and "A protein having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new antigen that is precipitously or progressively unrecognizable by any of the antibodies..." (p. 24). It is not always possible to make antibodies or protect against infection if the antigenic determinants have been altered.

the recitation of "mutants thereof" encompasses the deletion, substitution or insertion of any combination thereof protein, therefore any amino acid is being claimed, and no specific location for where the deletion, substitution or

insertion or any combination thereof within the synthetic peptide is recited, if all the amino acids are deleted or substituted or inserted the resulting synthetic peptide could result in a peptide not taught and enabled by the specification.

Thomas E. Creighton, in his book, "Proteins: Structures and Molecular Properties, 1984",(pages 314-315) teaches that variation of the primary structure of a protein can result in an instable molecule. He teaches that a single amino acid change can cause a mutant hemoglobin to have lower stabilities due to any of several causes:

1) alteration of close-packing of the interior; loss of one group that normally participates in a hydrogen bond or salt bridge;

2) the introduction of a charged or polar group into the interior or the insertion into a helical region of a Proline residue, which must distort the alpha-helix;

3) while sometimes radical changes of surface groups, even introduction of a non-polar side chain- have no great effect on stability.

Thomas E. Creighton, in his book "Protein structure: A Practical Approach, 1989; pages 184-186" teaches that present day site directed mutagenesis of a gene allows any amino acid in a protein sequence to be changed to any other, as well as introducing deletions and insertions. The reference goes on to teach that it is difficult to know which amino acid to change and which is the best residue to substitute for the desired functional and structural effect.

Nosoh, Y. et al in "Protein Stability and Stabilization through Protein Engineering, 1991" (chapter 7, page 197, second paragraph) adds support to Thomas E. Creighton, by teaching that results so far accumulated on the stability and stabilization of proteins appear to indicate that the strategy for stabilizing proteins differ from protein to protein and that any generalized mechanisms for protein stability have not yet been presented.

The substitution of any amino acid in any location within the synthetic peptide would not predictably result in a stable molecule. The specification only teaches the modification of side chains and states that natural or unnatural amino acids and/or their derivatives during peptide synthesis and the use of cross linkers and other method which impose conformational constraint

on the peptides or their analogs can be used. Specific amino acids in specific locations which result in stable mutations are not taught.

The scope of the claims (particularly with regard to the recitation of "fragments thereof" and "mutant thereof") is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of fragments or mutants of a polypeptide broadly encompassed by the claims and the claims broadly encompass a significant number of inoperative species. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and still retain similar activity/utility requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, the problem of predicting protein structure from mere sequence data of a single protein and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and finally what changes can be tolerated with respect thereto is extremely complex and well outside the realm of routine experimentation.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications of other types and the positions within the protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining similar activity/utility are limited in any protein and the result of such modifications is unpredictable based on the instant disclosure.

One skilled in the art would expect any tolerance to modification shown for a given protein to diminish with each further and additional modification, e.g. multiple substitutions. The sequence of some proteins is highly conserved and one skilled in the art would not expect tolerance to any amino acids modification in such proteins.

The specification does not support the broad scope of the claims which encompass all modifications and fragments because the specification does not disclose the following :

- the general tolerance to modification and extent of such tolerance;

- specific positions and regions of the sequence(s) which can be predictably modified and which regions are critical;

- what fragments, if any, can be made which retain the biological activity of the intact protein; and

- the specification provide essentially no guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed protein in manner reasonably correlated with the scope of the claims broadly including any number of additions, deletions or substitutions and fragments of any size. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, the changes which can be made in the proteins structure and still maintain activity/utility is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991) at 18 USPQ2d 1026-1027 and Ex parte Forman, 230 U.S.P.Q. 546 (Bd. Pat. App. & Int. 1986).

7. Claims 40, 45, 46, 51, 59 and 60 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Tabaqchali et al.

Tabaqchali et al disclose nucleotide sequences characterized in that it comprises a part or fragment of the nucleic sequence (2622-2693) corresponding to the gene known as UreI.

The prior art, Tabaqchali et al, discloses polypeptides, which appears to be the same as the claimed invention. Therefore, the prior art polypeptides appear to be the same, with any other identifying characteristics inherent in them. The art anticipates the claimed invention because the

claims recite any part or fragment thereof of the claimed sequence; it covers virtually any portion of the amino acid sequence.

And if the prior art products, polypeptides, are not the same as that claimed, they are obvious variations of that claimed, which the teachings of the prior art would have reasonably suggested to one of ordinary skill in the art at the time the invention was made, to use the disclosed genes to express the claimed polypeptides, making the claimed invention, as a whole prima facie obvious to one of ordinary skill in the art at the time the invention was made. It would have been obvious to a person of ordinary skill in the art at the time the invention was made that the polypeptide corresponding to the sequence disclosed in the art can easily be derived.

Since the Office does not have the facilities for examining and comparing applicants' disclosed polypeptides and the disclosed polypeptides of the prior art the burden is on applicant to show a novel or unobvious differences between the claimed polypeptide and the disclosed polypeptides of the prior art (i.e., that the disclosed polypeptides of the prior art does not possess the same material structural and functional characteristics of the claimed polypeptides). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Applicants have asserted that the prior art source was not *H. pylori* and that the sequences are not the same. However, the claims recite the Ure polypeptides disclosed in the art. The source of the polypeptides is not recited in the claims, and further the claims recite "or fragment thereof".

Applicants have referred the Examiner to pp. 4-5 of the instant specification, however these pages have been canceled. Applicants have asserted that it is unclear how a NT sequence of only 71 NT can be said to correspond to a gene composed of 584 NT. However, it is noted that the claims are directed to the polypeptide or any part of at least one of these polypeptides which prior art encompasses. Applicants have asserted that the prior art does not teach the amino acid which corresponds to the NT 2622-2693. The NT correspond to the ureI, only part of it as Applicants have claimed.

8. Claims 40-61 are rejected under 35 U.S.C. 102(a) as anticipated by or, in the alternative, under 35 U.S.C. 103 as obvious over Cussac et al.

It is noted that the authorship is not the same as the inventive entity and that it is unclear exactly when this reference was published.

Cussac et al disclose Ure genes from *H. pylori* and the expression of these genes in *C. Jejuni* or *E. Coli* (abstract).

The prior art, Cussac et al, discloses polypeptides, which appears to be the same as the claimed invention. Therefore, the prior art polypeptides appear to be the same, with any other identifying characteristics inherent in them. The art anticipates the claimed invention because the claims recite any part of the claimed sequence; it covers virtually any portion of the amino acid sequence.

And if the prior art products are not the same as that claimed, they are obvious variations of that claimed, which the teachings of the prior art would have reasonably suggested to one of ordinary skill in the art at the time the invention was made, to use the disclosed genes to express the claimed polypeptides, and make antibodies that bind the polypeptides, making the claimed invention, as a whole prima facie obvious to one of ordinary skill in the art at the time the invention was made. It would have been obvious to a person of ordinary skill in the art at the time the invention was made that the polypeptide corresponding to the sequence disclosed in the art can easily be derived.

Since the Office does not have the facilities for examining and comparing applicants' disclosed polypeptides and the disclosed polypeptides of the prior art the burden is on applicant to show a novel or unobvious differences between the claimed products and the disclosed products of the prior art (i.e., that the disclosed products of the prior art does not possess the same material structural and functional characteristics of the claimed products). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

9. Claims 53-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cussac et al taken with Sevier .

Cussac et al disclose Ure genes from *H. pylori* and the expression of these genes in *C. Jejuni* or *E. Coli* (abstract).

Sevier et al. teach the use of antibodies for immunodiagnositics or immunotherapy (abstract; p. 1800; 1802). It would have been obvious to a person of ordinary skill in the art the time the invention was made to use the polypeptides as taught in the prior art with the expectation of obtaining antibodies to the claimed polypeptides. Further, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to use the polypeptides in a composition to treat infection due to *H. pylori* since Cussac et al teach that these polypeptides can "...be useful in animal model for addressing the role of urease in the establishment and the maintenance of *H. pylori* infection." (abstract). The claimed invention is prima facie obvious in view of the prior art, absent any convincing evidence to the contrary.

10. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: The specification does not provide support for the recitation of a "pharmaceutically acceptable carrier".

11. The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record in previous Office Actions.

12. No claims are allowed.

13. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to N. M. Minnifield whose telephone number is (703) 305-3394. The examiner can normally be reached on Monday-Thursday from 7:00 AM-4:30 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula K. Hutzell, Ph.D., can be reached on (703) 308-3153. The fax phone number for this Group is (703) 305-3014 or (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

N. M. Minnifield

July 23, 1997

NITA MINNIFIELD
PATENT EXAMINER
GROUP 1800